SYPHILITIC INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

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THERE have been no more remarkable years in medicine than the last decade. In 1903 Metchnikoff infected apes with lues, thus robbing syphilis of its mystery and giving it a definite standing among infectious diseases. Schaudinn discovered the *spirochæta pallida* in 1905, while Wassermann announced his famous reaction in 1906, and Ehrlich gave to the world salvarsan, that synthetic substance that possesses a unique dual property, viz., a remarkable spirocheticidal activity and an absolute innocuousness to the infected tissues, in 1909. These notable results would seem to have followed each other in an ordered sequence and thus prepared the way for the no less brilliant researches of Noguchi and his co-labourers. In 1912, the former discovered the pallida present in twelve out of seventy paretic brains he was investigating. In a later report, he states that he has examined two hundred brains of paretics and twelve spinal cords of tabetics; the spirochetes were found in forty-eight brains of the former and one spinal cord of the latter.*

These findings have greatly simplified the complex problem of syphilogenous nervous disease. Paresis and tabes are the direct result of the action of the pallida on the cortical and spinal neurons. This underlying pathological process is not found in other forms of syphilitic nervous disease, although the lesions of paresis have been observed coëxisting side by side with those of cerebral and tertiary syphilis. While Fournier's theory of parasyphilis is, in the light of recent researches, no longer tenable, yet there still remain certain

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*Marinesco has found the spirochetes in the cortex in 2 out of 26 paretic brains he has examined. Forster and Tomasczewski, after the method of brain puncture devised by Neisser and Pollak in living subjects, have succeeded in demonstrating by dark ground illumination, active spirochetes in 8 out of 20 cases investigated. Levaditi, Marie and Banchowski have recently demonstrated (July, 1913) the spirochetes in brains freshly obtained, in 8 out of 9 cases of general paralysis. They prefer the ultramicroscope. They have also used staining with India ink and Fontana's method (a modified silver process) with positive results.

difficulties awaiting solution. Why are the pathological findings in paresis and tabes so absolutely distinctive? And why do they differ so radically from those observed in nervous syphilis? Can it be due to the personal equation, or to the neurotoxic action on the part of the spirochetes? The following facts are suggestive of the latter theory: According to Morel-Lavallée, Bélières and Bouvaist, six men infected with lues from the same woman all developed paresis. Of three men, says Nonne, who were infected in one night by the same person, one developed tabes and two paresis. Erb states that five men obtained their tabes and paresis from the same source (Kræpelin). Brosius mentions five glass blowers who contracted simultaneously a chancre of the lip from their occupation, of whom four developed tabes and one paresis. The simple fact would seem to be that nervous syphilis, paresis and tabes are but varied expressions of a far reaching reaction to the spirochæta pallida. General paralysis, says Robertson, is one of the manifestations of active syphilis. Marinesco believes that in paresis we are "face to face with the results of the direct action of the spirochæta on the cells of the brain cortex." Tabes and paresis are one and the same disease differing only in location, extent and intensity of the process. Nageotte regards these diseases as pathologically identical, the clinical aspect being determined by the initial localization.

Diffuseness is a distinguishing characteristic of nervous syphilis. While the clinical syndrome may indicate that the brain or cord is the chief seat of attack, yet as a rule the entire nervous system is to a greater or less degree affected. Commonly it manifests itself within the first ten years following infection, occurring most frequently between the third and fourth year. Out of three hundred and thirty-five cases investigated by Nauyn, forty-eight per cent. developed symptoms of cerebral lues during the third year (Gregory and Karpas). Recently I reported a case of acute syphilitic myelitis that developed four months after exposure. Tourette has reported a case of cerebrospinal lues that occurred two months after infection. Paresis and tabes, on the other hand, do not usually occur before the tenth or twentieth year after infection. Paresis is unusual before thirty years of age, fairly frequent after fifty (Kræpelin). In sixty-five cases of tabes, Mott found the average age of onset to be thirty-seven years; the average interval of infection in one-half of these was fifteen years, while the shortest was four.

Nervous syphilis (acquired) manifests itself in two ways: First, "those redoubtable cerebrospinal localizations," says Chauf-

fard, "which constitute the darkest chapter in the history of syphilis," viz., inflammatory affections of the membranes, vascular syphilis, tertiary manifestations, arteriosclerosis and multiple neuritis. Second, progressive neuronic degeneration of certain neural systems, as the sensory neurons in tabes, and a more diffuse involvement in paresis and a combination of both of these morbid activities in taboparesis. The lesions in acquired syphilis are arteritis, thrombosis, cerebral meningitis, meningomyelitis, acute myelitis, meningitis and gumma; the more usual being basilar meningitis and meningomyelitis. Certain chronic conditions sometimes observed in the kidneys, liver and myocardium are explicable along the line of an old forgotten syphilis.

The differentiation of these various specific affections is frequently a matter of great difficulty. The researches of Wassermann, Nonne, Noguchi, etc., have greatly simplified the problem. Laboratory methods and the clinical syndrome are both needed to arrive at a diagnosis.

THE WASSERMANN REACTION. Its importance for diagnostic and therapeutic purposes cannot be over-estimated (Ehrlich). No examination can be considered final unless the four reactions of Nonne are employed, viz., Wassermann (blood serum and spinal fluid), lymphocyte count, and globulin reaction. Nonne has emphasized the fact that the Wassermann reaction is only a symptom and its absence does not invalidate the diagnosis. It is present in from eighty to ninety per cent. of syphilitics. In early nervous syphilis it is found in one hundred per cent. of the cases, in its secondary and tertiary forms the percentage may fall to seventy, and during the latest period it may reach fifty (Jelliffe). The results obtained from the original Wassermann, where only 0·2 cc. of spinal fluid is used differ radically from those obtained by Hauptmann's modification, in which increasing strengths of spinal fluid are employed. In the latter all forms of nervous syphilis, viz., cerebrospinal lues, paresis and tabes, give a positive reaction; in the former, paresis is uniformly positive, tabes not quite so constant, and cerebrospinal lues is negative. General syphilis without involvement of the nervous system gives a negative reaction even with the larger quantities of fluid.*

*Lange's colloidal gold test. Recently certain writers have called attention to this test which they regard as more delicate than those heretofore in use. To a certain amount of cerebrospinal fluid of a paretic is added in the presence of 0·4 of sodium chloride, colloidal gold solution. There results a certain change in colour which is absolutely characteristic of paresis. The tabetic spinal fluid is quite distinctive but not pathognomonic; cerebrospinal syphilis reacts in about the same dilutions. Non-specific cases either failed to react or reacted at different dilutions.

LYMPHOCYTOSIS. Ten lymphocytes to the c.mm. is pathological. Sicard, also Ravaut, have called attention to the fact that pleocytosis may antedate all neurological symptoms; it has been observed as much as two years before the manifestation of the disease (Jelliffe). According to Mott, the membranes are affected at the time of the appearance of the cutaneous rash. Lymphocytosis is not limited to nervous syphilis, and by this term I mean both the non-degenerative and the degenerative forms of the disease (paresis and tabes). It is often seen in tubercular meningitis, in essential epilepsy, multiple sclerosis, etc. The absence of lymphocytosis does not negative the presence of paresis, since it is known to be absent in 10 per cent. of these cases; it is, however, one of the earliest and most reliable indications of the onset of both paresis or tabes. In one of Boyd's cases of the former, the cell increase was three thousand four hundred.

THE DETERMINATION OF GLOBULIN CONTENT.—In the neuroses or in healthy people this reaction does not occur; in other forms of nervous disease, it is not infrequently seen, while in cerebrospinal syphilis, paresis and tabes, it is rarely absent. Globulin excess is observed in spinal tumours, both specific and non-specific; it bears a distinct relation to lymphocytosis but not to the Wassermann reaction. The Nonne-Apelt and Noguchi reactions indicate simply globulin excess. Nonne's Phase I consists in mixing equal parts of spinal fluid and a neutral solution of ammonium sulphate. If the fluid becomes milky or cloudy within three minutes, the test is positive. Noguchi's butyric acid test* causes a definite, flocculent precipitate either immediately or within two hours if globulin excess is present; in my own experience, it has been more sensitive and reliable than Nonne's Phase I. According to the latter, Phase I is never present in a luetic unless the nervous system is involved.

THE DEGENERATIVE PHASE OF NERVOUS SYPHILIS: PARESIS AND TABES. Fisher estimates that from 10 to 15 per cent. of luetics develop this type. Robertson says that from 3 to 5 per cent. of all syphilitics, or from 9 to 15 per cent. of those who have not recovered after the lapse of five years, result in paresis or tabes. Mœbius styles paresis tabes of the cerebral cortex. Of two hundred and thirty-six cases of tabes analyzed by Byrom Bramwell, 11·4 per cent. became paretic. According to Mott, 10 per cent. of general paralytics are of the tabetic type. Ten per cent. of five hundred

*To 2 c.cm. of cerebrospinal fluid add 5 c.cm. of 10% butyric acid with the application of heat: to this add 1 c.cm. of a 4% solution of sodium hydrate with the further application of heat.

cases studied by him showed marked sclerosis of the posterior columns. Fürstner is inclined to the opinion that the spinal cord is always affected in paresis, and Raymond and Nageotte assert that every paretic would show tabetic symptoms if he lived long enough.

According to Kræpelin, from 10 to 20 per cent. of asylum admissions are paretics, and it has attained its present frequency in our day. Over 13 per cent of all cases admitted to the New York State insane asylums in 1911 were cases of paresis. In Philadelphia the cases of paresis, tabes and cerebrospinal lues admitted to the neurological wards form 15 per cent. of the admissions. There has been in England a marked increase in the industrial and mining regions, and a decrease in the agricultural. It occurs more frequently in men, the ratio varying from one to four, to one to seven. In the opinion, however, of Dr. George T. Mills, of the Central Islip State Hospital, New York, this disparity does not exist, the ratio is practically the same. Hoppe finds from the figures of Altscherbitz, that one case of paresis occurs to every three thousand people in the city, while in the country only one in every nine thousand is affected. Among prostitutes, 58·5 per cent. of deaths are due to this disease (Kræpelin). Chiarugi and Haslam and Esquirol were the first to give a description of *dementia paralytica.* Bayle, in 1822, and Georget and Calmeil, in 1825, gave the first accurate portrayal of its mental and physical symptoms, thus creating a new clinical syndrome which was not, however, kindly accepted by all alienists. Griesinger regarded it as simply a combination of mental diseases, and even to-day, says Kræpelin, there are still those who look upon it as a composite of mental diseases rather than a morbid entity with a distinct anatomo-pathological basis, which makes it one of the best recognized diseases in all medicine.

Griesinger's mental attitude finds a ready explanation in the kaleidoscopic character of the mental symptoms. No description can embrace all the confusing vagaries; the symptoms may simulate those of any of the well-known forms of insanity. "Any mental complex," says Smith, "can be present in general paresis." The basic fact is a *peculiar progressive mental weakness,* and on this foundation of dementia are grouped a great variety of psychotic symptoms changeable as the sand dunes of Cape Cod, varying from month to month, and even from day to day. The conventional clinical forms are only arbitrary groups adopted for convenience, the better to facilitate the description of the clinical features of this disease. *None of them runs absolutely true,* the distinctive feature being a

slowly developing dementia associated with an organic brain disease and characteristic pathological findings.

There are three types, viz., the demented, depressed and grandiose. These paretic syndromes are often preceded by a preparetic or preliminary period. From the laboratory findings at this stage one may be able to predicate the appearance of paresis months or years before its evolution. Frequently the symptoms at this time are those of neurasthenia. There is marked fatigability, insomnia, irritability, lack of initiative and of concentration. The patient is less alert and keen than formerly and is absent-minded; there is moral deterioration; he indulges in all kinds of excess; is untidy and careless about his personal appearance; judgement is impaired, and the characteristic psychic weakness is clearly evident. The perceptions are very early at fault; the mental reflexes are sluggish, he cannot grasp details, is inattentive, indifferent, loses himself even among familiar surroundings, and acts as though he were mildly intoxicated or in a dream. The association of ideas is impaired, those most used being the longest preserved. The insane beliefs may all be present although illusions and hallucinations play but a minor part; delusions are almost invariable, with occasional exceptions in the dementing form. Illusions of hearing are more frequent than those of sight; hallucinations of taste and smell, while sometimes seen, are not as prominent as those of sight. Memory defects are common, especially those pertaining to recent events. There is marked difficulty in calculation; ridiculous mistakes are made in the simplest problems. As the disease progresses memory becomes totally lost.

The fantastic character of the delusions is an index of the degree of the dementia. Kræpelin refers to disturbances of will such as are seen in catatonics, viz., catalepsy, echolalia, verbigeration, resistiveness, stereotyped movements, etc., but says that he does not feel justified in creating a special catatonic form of this disease. Criminal actions are not unusual, such as sexual misdemeanors, purposeless stealing, homicides, etc. Suicide must always be kept in mind. There is a liability to senseless whims and impulsive actions; one of Kræpelin's cases stepped out of a second story window to pick up a cigar stump he noticed on the sidewalk below him. There is frequently observed a bustling, meaningless business activity and a constant letter writing. The nervous symptoms are of greater importance and give "the particular stamp to the disease." A severe initial headache is usual, dull in character. The brain feels as though it were pressed upon by a heavy

weight. Word deafness, word blindness, hemianopsia, apraxia, auditory hallucinations, etc., point to the involvement of definite cortical areas. Optic atrophy is observed in from 4 to 20 per cent. of the cases, notably those where the posterior columns are degenerated (Kræpelin, Mölis, Osler, Norris, and Oliver). Martins notes a loss of ability to recognize the taste of salt, Toulouse states a third of his cases were unable to perceive the smell of camphor. In posterior cord involvement, the sensory disturbances are characteristic of tabes; as the disease progresses all forms of cutaneous sensibility are affected. If the patient's attention is diverted, one may stick a pin through the skin without his knowing it. The loss of sensibility applies to the internal organs as well and should always be kept in mind, since only in this way can burns and serious injuries be avoided. Pneumonia may run its course without even being recognized. The face is expressionless, and both it and the tongue are subject to fibrillary tremors. The voice is monotonous; the loss of resonance is often the first symptom observed in singers. In advanced cases a persistent, rhythmic grinding of the teeth is almost invariably observed. Aphasia, paraphasia, and disturbances of articulation and of writing are of very common occurrence in this disease. Pupillary disturbances are most frequent, viz., deficiency in size, distortions of the pupillary outlines, loss of consensual light reflex and Argyll-Robertson pupil, the latter occurring in from 50 to 70 per cent. of the cases (Westphal, Räcke, Siemerling, Franz). *The Argyll-Robertson pupil means simply that the nervous system has been infected with lues; it is not pathognomonic of paresis.* It is, however, a warning of the danger of paresis and tabes (Gowers, Babinski).

A sluggish light reflex is an incomplete stage of the Argyll-Robertson pupil and is frequently seen in incipient paresis. Loss of light reflex is due to the action of a particular toxin on certain nerve cells or fibres, the exact position of which is still a matter of doubt; *it is not always due to an actual degeneration, since it may come and go from time to time* (Robertson). Argyll-Robertson pupil may occur in acute alcoholism and hysteria. Loss of sensory light reflex—a dilation caused by pain as from a prick of a pin near the eye—Bevan Lewis regards as one of the earliest pupillary symptoms in paresis. Loss of light reflex and accommodation may occur at the same time or accommodation alone be lost.

Most important of the motor disorders are the epileptiform and apoplectiform seizures; the former usually manifest themselves as a cortical epilepsy, less frequently there is a severe general convulsion. The body temperature is generally elevated during a seizure.

From twenty to one hundred attacks may occur in twenty-four hours, and the seizures may occur continuously for a fortnight. Almost invariably after the cessation of these attacks, there is a decided increase of the mental weakness. The apoplectiform seizures occur suddenly with loss of consciousness, stertor, coma, rigidity or flaccid paralysis; there may or may not be residuals. On the sensory side there are similar attacks—psychic equivalents, characteristic of essential epilepsy. Any of these forms may occur at any stage of the disease. The apoplectiform attacks belong usually to its earlier period; in the beginning they are usually light and become more severe as the disease progresses. Paretic seizures are probably the result of new invasions of the organism rather than due to vague metabolic changes and cerebral congestion (Moore).

In 75 per cent. of the cases of paresis, the knee-jerks are exaggerated, sluggish or lost (Franz); when exaggerated, the Babinski and ankle clonus are often present. There is a difference between the two sides in 18 per cent. of the cases (Räche). The Achilles jerk disappears before the knee-jerk. De Montyel found the sexual power lost in 79 per cent. and increased in 15 per cent. of his cases. The liability to broken bones, hematoma of the ear, and pneumonia, cannot be too strongly emphasized; the hematoma auris and fragility of the bones are due to the deranged metabolism of the paretic. Temperature variations are usual; the two sides of the body may show a difference; there may be a marked elevation without any appreciable cause; in a certain proportion of the cases, it is the direct result of the brain lesion, more frequently it is due to constipation, a distended bladder, broken ribs, or pneumonia; toward the close of life it is subnormal. Sleep is greatly disturbed in the beginning and during the excited stage; later there may be somnolence so that the patient is awake only when eating or being talked to. The appetite is greatly impaired at first, the patient losing weight until the acuteness of his illness is past; later it becomes ravenous and there is rapid taking on of flesh—the obesity peculiar to paresis. The end is characterized by extreme wasting.

Our review of the various types will be as brief as a fair degree of accuracy will permit. Fortunately, thanks to the kindly courtesy of your asylum authorities, we shall be able with these five patients to illustrate quite freely the clinical syndrome of this disease.*

*Through the courtesy of the first assistant physician of the Brandon Asylum who placed at our disposal five patients for the purpose, we were enabled to present many of the clinical aspects of paresis in a very satisfactory manner. Three of the patients were clearly paretic, one was doubtful and one a case of cerebrospinal lues.

THE DEMENTED TYPE. Progressive mental deterioration with motor paralysis is its salient feature. The intellectual and social fabric speedily crumbles to ruins; mental dullness, loss of concentration, moodiness, irritability, confusion, disorientation, inability to recognize those around them, are some of its chief characteristics. Convulsions are more frequent and remissions more rare than in the other varieties. Transient delusional states are common. They may be suicidal. Depressed and expansive states at times assume marked prominence. They are gluttonous and their desire for drink is inordinate. This form comprises 53 per cent. of Kræpelin's Heidelberg cases.

THE MELANCHOLIC TYPE. This possesses in a great degree many of the features of the depressive phase of manic-depressive insanity with mental deterioration superadded. The patient is a prey to all kinds of hypochondrial ideas and is subject to vague and indefinite sensory perversions. The delusions may be either accusatory or persecutory, and are often accompanied by hallucinations, especially of hearing. There may occur grandiose ideas, stupor or periods of intense anxiety. A marked catatonic state is sometimes present. Convulsions are more rare and the duration of life less than in the preceding type. Twelve of Kræpelin's Heidelberg series belonged to this group.

GRANDIOSE FORM (classical paresis). Either depression or exaltation may be the first symptom. These patients always "feel fine" and revel in grandiose ideas of the most senseless and fantastic nature; as illustrated by our patient with his bank of gold, dreadnaughts and other wonderful possessions. A patient of mine in the last stage, helpless and confined to bed, said he could whip Corbett and saw seven cords of wood daily; another stated he had a horse that could trot across the Atlantic in three minutes, and still another was in the habit of giving me million dollar checks when I called. The grandiose ideas are not so marked in women as in men. Paretics are readily distractible; a little skillful suggestion will turn their morbid fancies in any direction. They are liable to attacks of great excitement, when they are dangerous as wild animals. Hallucinations are not infrequent. The excitation may be tinged with a fringe of depression or hypochondriasis, indeed the clinical picture may for a time assume the typical characteristics of the manic-depressive syndrome. There is a blunting of the moral sense and a loss of all regard for personal appearance. The exaltation may last for years or it may recede, and were it not for the intellectual impairment the patient might be considered prac-

tically normal. The group comprises 36·3 per cent. of the Heidelberg series, and very properly includes the agitated type, since the latter is only the expansive form pursuing a stormy course. The most excited cases are called "galloping paresis," and because of the intense excitement they quickly become exhausted and die in a few days or weeks. Convulsions are less common and remissions more frequent than in the preceding groups.

Juvenile paresis differs from that of the adult form chiefly as to time of incidence and nature of the clinical syndrome. The pathological findings are the same in both. It develops usually during adolescence, although it may occur between the fifth and sixth year. There are often notable physical and mental defects in the child preceding the manifestation of the disease. Children who dement without apparent cause are probably instances of this condition as are also the so-called "dementias associated with epilepsy" in childhood. The clinical symptoms, while often those of the dementing form, frequently are so vague and indefinite that only by the aid of laboratory methods is it possible to arrive at a diagnosis. Convulsions are very frequent. Kræpelin reports four hundred and fifty in a single week in one of his patients.

The termination of these mental complexes constituting paresis is ultimately death. Dementia becomes absolute, there is extreme wasting and existence is purely vegetative; cardiac failure ends the tragedy.

The duration of paresis may vary from a few months to many years (thirty-two years, Alzheimer's case). Fifty per cent. die in one year; 75 per cent. in two years, 90 per cent. in three years (Robinson). Remissions occur in 20 per cent. of the cases; they are seen in all forms, but are most frequent in the grandiose type. They may occur suddenly or be of gradual evolution. It is usually a matter of weeks or months for the remission to reach its full development, and its duration is usually of a few months; three or four years is uncommon, while many years is most exceptional. Among these latter are Halban's patient, eight years, Dobrschansky's fourteen years, and Tuzcek's twenty years.

According to Nissel and Alzheimer, there is in paresis a definite anatomical process which is not found in other forms of nervous syphilis (Jelliffe). In long-standing cases the brain is atrophied and the dura is adherent in patches to the skull. The cortex is greatly shrunken so that its breadth is reduced often by one-half, and the destruction taking place in it is greater than in any other disease. The pia is cloudy, thickened, infiltrated and adherent, so

that when it is removed the cortex is badly lacerated. Periarteritis and infiltrations by lymphocytes is usual. The ventricles are dilated and the ependyma is covered with hyperplastic granulations of neuroglia. Taken singly, the changes in the cortex have no differential significance since they may be observed in other diseases, but when considered in their totality they are diagnostic of paresis. Accumulations of plasma cells in vessel sheathes are of all cortical changes the most important, because they are never absent in general paralysis, and they show a characteristic distribution. Rod cells in the neighbourhood of the vessels are seen in other diseases but in smaller numbers and not remote from the meninges as in this disease (Kræpelin). New vessel formation, endothelial proliferations, grave cell alterations, with the associate destruction of nerve fibres and neuroglia overgrowth, all add to the completeness of this pathologic picture. Loss of nervous tissue is generally accompanied by a corresponding increase of the neuroglia. Similar, but not so severe changes, are seen in the cerebellum, basal glanglia, pons, medulla, spinal cord, sympathetic ganglia, peripheral nerves, etc. Straub found in 82 per cent. of his cases a diseased aorta. The bones and body viscera are usually affected in a marked degree.

The diagnosis of paresis is frequently beset with great difficulty: a mental trouble occurring in a middle-aged man for the first time should suggest paresis, especially if there is a history of a previous lues. The mental symptoms may be so varied, confused and shifting that they suggest a combination of "disease pictures" rather than one of the best know types in psychiatry. Each clinical form may, chameleon-like, assume the characteristics of any of the others. But of still more importance are the neurological signs, chief among which are Argyll-Robertson pupil and irregularity of outline of pupil, optic atrophy, sensory disturbances, notably hypalgesia during inattention, speech defects (awkward and anxious patients often show these resembling paresis), loss and exaggeration of knee-jerk, epileptic and apoplectiform seizures, etc., some of which may precede by years the onset of the disease. They are probably the index of a syphilized nervous system, the degenerative process not yet having begun. That the diagnosis of paresis cannot be made with accuracy from the clinical syndrome is shown by Southard who followed to the post-mortem room and laboratory forty-one well marked cases in which the entire medical staff of the asylum agreed that on clinical grounds the diagnosis of paresis was certain. His examination proved that there were six errors, or 15 per cent. If incipient cases were included with those that are

well marked the error would certainly be very much greater. It is only by calling to our aid the sero-biological reactions that we can with any certainty arrive at a diagnosis. When all four reactions are positive, especially if small quantities of spinal fluid—from ·05 to ·2 cc. (Jelliffe)—are used, the case is almost invariably one of paresis. A positive reaction on the part of the blood serum and spinal fluid may occur in all forms of nervous syphilis—in cerebrospinal lues, paresis and tabes, and under such conditions it must be interpreted in the light of the clinical symptoms. Both fluids may give a negative reaction in stationary paresis. In one per cent. of the cases the blood serum, and in six per cent. the spinal fluid, reacts negatively (Robertson). Occasionally the reaction is that indicative of cerebrospinal syphilis, viz., positive blood serum with lymphocytosis and globulin excess. The diagnosis of paresis, which is equivalent to passing a death sentence, should not in our present state of knowledge be lightly made.

The abolition of paresis lies in the prevention of syphilis, and writers are sadly at variance as to whether antisyphilitic treatment will prevent paresis. Fournier believed it possible. According to him only five per cent. of syphilitics received adequate treatment, while on the other hand, Kriss, Schuster and Junius and Arndt are far from being convinced as to this efficacy of mercurial treatment. The early recognition, in the so-called preparetic stage, probably the incipient period of the degenerative process, is of great importance, since this is the one time favourable for successful therapy. Availing ourselves of the modern methods, we should be governed by Fournier's dictum: "*Strike hard, quick and often.*"

In the presence of paresis and tabes, there is some excuse for therapeutic nihilism. The former is more intractable than the latter to treatment, and both are much less amenable than the other forms of nervous syphilis. Generally speaking, the longer syphilis has existed the more resistent it is to treatment, and paresis is one of its late manifestations. Jelliffe aptly says: "It is a question of the inaccessible spirochete." Its habitat in paresis is at a distance from blood vessels and lymph channels; the latter being obstructed interferes with flow of lymph as well as the transmission of therapeutic agents. Thus, the pallida unmolested works out its lethal purpose.

Remissions are nature's attempt at a cure. They develop spontaneously, natural episodes as it were in the course of the disease. The quiet and regular hours of a hospital regime are conducive to their occurrence. Various therapeutic measures, it would seem,

are capable of artificially inducing them; viz., first, the prolonged injection of small doses of tuberculin, from 0·01 to 0·1 mg.; second, the injection of bacterial toxins. Kræpelin suggests that since septic organisms hinder the propagation of the spirochetes, it may be possible to use them as allies in the fight against paresis. Third, the use of nucleic acid and metallic ferments. Fischer, every three to five days, injects his paretics with 0·5 gramme of the sodium salt of nucleinic acid in 10 per cent solution. He reports four remissions as following this treatment in twenty-two cases. Thus it is believed that by the use of these agents we produce leucocytosis and stimulate the natural defense of the organism against the spirochetal onset. The period during a remission, when all medical care and oversight are discarded because they are considered irksome and unnecessary, is in reality the time when treatment should be most vigorously pushed. At present the cure of paresis can neither be affirmed or denied. An ambition to accomplish this will ever be the best stimulant to a persistent endeavour. There is not the slightest doubt that treatment can influence, even if it does not arrest, the paretic process, as is shown by a decrease in lymphocytosis and a diminution in the intensity of the Wassermann reaction. This may become negative and remain so a year or more, as it did in Alt and Willig's cases.

When we recall what has been accomplished in that hitherto incurable disease, sleeping sickness, one ought not utterly to despair of paresis. In the last few years, Martin, in the Pasteur Hospital in Paris, has treated forty cases of the former; of the first twenty patients, eleven died; of the next ten four died, while all of the last ten cases recovered. Two patients of the last series were under treatment for more than three years. These remarkable results were due to improvement in the method of treatment (Chauffard).

Since in paresis we are dealing with a desperate disease, Robertson believes that we are justified in employing desperate remedies; that we should be governed by the same principle that influences the surgeon in hopeless conditions: while he counts on almost a certain fatality, he feels justified in assuming the risk. The ethics in each instance are the same, and we should not hesitate at radical procedure even though death sometimes result.

The administration of salvarsan is not without danger. Gibbard and Harrison are authority for the statement that up to 1912 about one hundred and fifty deaths have been due to it, but that during the same period less than a dozen have died from the Herxheimer reaction, and they do not agree with Ehrlich's opinion

that this is due to a liberation of endotoxins, but rather to an overdosing with salvarsan of a patient peculiarly sensitive to arsenical preparations. According to them also, the neurorecidives are not in any sense a neurotrophic action of salvarsan, but should be regarded as evidences of a syphilitic relapse.

Since the researches of Noguchi and Moore and Marinesco, my views in regard to therapy have undergone a radical change. My conviction is that in every case except the very advanced, modern methods of treatment should be vigorously applied; nothing could be more absolutely futile, even fatuous, than the routine use of the combined treatment so generally used. Long experience has demonstrated that mercury is of no value in clearly developed paresis. Kræpelin, indeed, believes it to be contra-indicated, as he has observed acute excitement with rapid loss of strength follow a course of inunctions. Bucholz also reports two cases of "galloping paresis" developing under the same conditions.

With rare exceptions the conventional dose of salvarsan, 0·6 gramme, may be given, always intravenously. Gennerich regards an intensive course of salvarsan as consisting of 4 grammes, while on the other hand Dreyfuss advises a maximum amount of from 6 to 9 grammes, distributed during a period of from eight to twelve weeks. Are we then justified in our endeavour to reach the spirochetes burrowing among the nerve cells in the cortex, in using or even in increasing these massive doses of Dreyfuss? Certainly the patient's welfare will be in no manner compromised, since untreated his malady has only one inevitable end—death.

THE INTRASPINOUS METHOD. The choroid plexus exerts a marked control over the composition of the cerebrospinal fluid (Flexner). Relatively few drugs are capable of passing this barrier; notable among these is urotropin which does so freely, while on the other hand potassium iodide entirely fails to do so. Only detectable quantities of arsenic, which quickly disappear, are observable after the intravenous injection of salvarsan. The cerebrospinal fluid occupies the subarachnoid spaces and communicates with the canalicular system surrounding the vessels and nerve cells of the brain and spinal cord (Mott), and furnishes the most direct path of access for curative agents. This fluid must be made the purveyor of these substances, for only in this way can we reach the otherwise inaccessible nervous tissues. The intraspinous method, therefore, is the logical procedure in the treatment of syphilitic infections of the central nervous system.

Experiments on rabbits have shown that arsenic injected intra-

spinally is a dangerous procedure and not to be considered; the only way to introduce it with safety into the rachidian fluid is by the use of salvarsanized serum.

Serum derived from patients suffering from secondary syphilis, who three days previously have been injected with salvarsan, or serum from the patient himself an hour after receiving an injection of 606, has been used intraspinously for the purpose of bringing the spirocheticidal action of the drug into immediate contact with the membranes. Robertson, of the Royal Asylum, Edinburgh, and Swift and Ellis, working in the Rockefeller Institute Hospital, have for some time been conducting some remarkable investigations along these lines. The former uses the salvarsanized serum in addition to, and in the intervals between, the salvarsan injections. The dose varies greatly, all the way from 3 to 30 cc. according to the technique employed in the preparation of the serum. The spirocheticidal action of the serum of salvarsan-treated patients is markedly increased by heating at 56° C. for thirty minutes (Swift and Ellis). Before making the injection, from 5 to 15 cc. of spinal fluid is withdrawn "until the pressure falls to 30 mm. of spinal fluid." The trying out of this method will require time and patience and will be watched with great interest.

NOTE.—Dr. Taylor informs me that in the out-patient department of neurology of the Massachusetts General Hospital, Dr. Ayer has for some months been using intraspinal injections, especially in the treatment of tabes, and that he has obtained certain definite results. Lymphocytosis may practically disappear and the Wassermann in the blood serum and spinal fluid may be changed to negative. Treatment does not seem to arrest the progress of optic atrophy in tabetics.

Myerson, of the Psychopathic Hospital, Boston, reports under observation seven cases of paresis in which there was no question as to diagnosis, and one case of "clinical paresis" in which the spinal fluid was negative; the possibility in this patient of cerebrospinal lues must be considered.

In all these cases the pathological process characteristic of general paresis was modified by the use of salvarsanized serum, and according to him the blood serum and spinal fluid may become negative and remain so indefinitely; there may also occur clinical betterment.

A well marked case of paresis, now under our care, has been remarkably benefited by the intraspinous method. Swift and Ellis in

the October issue of the *Journal of Experimental Medicine* express the opinion that we should "confine our efforts at the local therapy of syphilis of the central nervous system with salvarsan to the use of such salvarsanized serum."

To PROVE or disprove the value of strychnine as a rapid cardiac stimulant, Parkinson and Rowlands studied the immediate effect of the subcutaneous injection of one-fifteenth of a grain of strychnine sulphate on the blood pressure, rate and regularity of the pulse, rate of respiration, and the general condition, in a series of fifty patients presenting signs of severe heart failure. In one half of the cases the rhythm was regular, in the other half the auricles were fibrillating. MacKenzie's ink polygraph was used to record the pulse and respirations, and the mercurial sphygmomanometer devised by Leonard Hill was used to record the systolic blood pressure. Records of the pulse, respirations, and blood pressure were made immediately before the injection and every five minutes for an hour afterwards. No evidence of change in the blood pressure, rate of the pulse, rate of respiration, or general condition was found, and these workers conclude that strychnine has no effect which justifies its employment as a rapid cardiac stimulant in cases of heart failure.—Abstract, *Quarterly Journal of Medicine*, Vol. VII, No. 25.